## REMARKS

Applicants thank Examiner Bowman and Supervisory Examiner Schultz for the informative discussion and interview on June 22, 2009. Claim amendments and the rejections under 35 U.S.C. § 103(a) were discussed during the interview. The content of that discussion has been incorporated into the present response.

**Amendments to the claims**

With the present submission, claims 52-56 have been amended. Specifically, dependent claims 53-56 has been amended to refer back to claim 52, rather than to claim 1, which has been previously canceled. In claim 52, part (a) has been added to define the length of each strand. Claim 52 part (b), which was previously part (a), has been amended to include the option of universal base modifications and a terminal cap moiety at the 3'-end or 5'-end, as well as at both the 3' and 5'-ends of the sense strand. Claim 52 part (c), which was previously part (b), has been amended to include the options of 2'-deoxy and universal base modifications in the antisense strand. These amendments are supported by the instant specification as filed and detailed support is provided below.

The limitation of claim 52 part (a) *"each strand is between 18 and 27 nucleotides in length"* finds support at page 31, lines 3-6:

> In another embodiment, a chemically-modified siNA molecule of the invention comprises a duplex having two strands, one or both of which can be chemically-modified, wherein each strand is about 18 to about 27 (*e.g.*, about 18, 19, 20, 21, 22, 23, 24, 25, 26, or 27) nucleotides in length…

The limitation of claim 52 part (b) *"the sense strand comprises 10 or more 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, or universal base modified nucleotides, and a terminal cap molecule at the 3'-end, the 5'-end, or both 3' and 5'-ends of the sense strand"* and part (c) *"the antisense strand comprises 10 or more 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, or universal base modified nucleotides"* find support at page 28, lines 12-29:

> In one embodiment, the invention features a siNA molecule, wherein the sense strand comprises one or more, for example, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more phosphorothioate internucleotide linkages, and/or one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or about one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) universal base modified

> nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the sense strand; and wherein the antisense strand comprises about 1 to about 10 or more, specifically about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more phosphorothioate internucleotide linkages, and/or one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the antisense strand. In another embodiment, one or more, for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more, pyrimidine nucleotides of the sense and/or antisense siNA strand are chemically-modified with 2'-deoxy, 2'-O-methyl and/or 2'-deoxy-2'-fluoro nucleotides, with or without one or more, for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more, phosphorothioate internucleotide linkages and/or a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends, being present in the same or different strand.

This combination of features is well exemplified throughout the specification, for example in the motifs of Table IV (please see the replacement Table IV submitted with a preliminary amendment dated May 19, 2009), and in numerous exemplary sequences shown in Table I and the Figures. ***At least 84 sense strand sequences of Table I support and exemplify the claimed combination of features.*** *See, e.g.,* SEQ ID NOs: 311, 312, 319, 329, 335, 339, 341, 343, 345, 372, 373, 376, 377, 381, 382, 384, 385, 425, 427, 429, 431, 433, 435, 437, 439, 441, 443, 445, 447, 453, 455, 457, 459, 463, 465, 467, 471, 473, 475, 477, 479, 481, 483, 485, 487, 489, 491, 493, 495, 497, 499, 501, 503, 505, 609-614, 616-618, 630, 632, 634, 636, 638, 640, 642, 644, 646, 648, 650, 652, 654, 656, 658, 660, 662, 664, 665, 668, and 669. ***At least 73 antisense strand sequences of Table I support and exemplify the claimed combinations of features.*** *See, e.g.,* SEQ ID NOs: 317, 322, 332, 338, 340, 342, 344, 374, 375, 378, 379, 380, 383, 386, 387, 388, 389, 420, 450, 452, 454, 456, 458, 460, 466, 468, 472, 474, 476, 478, 480, 482, 484, 486, 488, 490, 492, 494, 496, 498, 500, 502, 504, 506, 575, 592-597, 601-606, 631, 633, 635, 637, 639, 641, 643, 645, 647, 649, 651, 653, 655, 657, 659, 661, and 663.

Support for dependent claims 53, 54, and 55 can be found in the same paragraph:

> In one embodiment, the invention features a siNA molecule, wherein the sense strand comprises one or more, for example, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more phosphorothioate internucleotide linkages, and/or one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or about one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) universal base modified

nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the sense strand; and wherein the antisense strand comprises about 1 to about 10 or more, specifically about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more phosphorothioate internucleotide linkages, and/or one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the antisense strand. In another embodiment, one or more, for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more, pyrimidine nucleotides of the sense and/or antisense siNA strand are chemically-modified with 2'-deoxy, 2'-O-methyl and/or 2'-deoxy-2'-fluoro nucleotides, with or without one or more, for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more, phosphorothioate internucleotide linkages and/or a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends, being present in the same or different strand.

Support for claim 56 is found at page 62, lines 16-21:

> In one embodiment, the invention features a composition comprising a siNA molecule of the invention, which can be chemically-modified, in a pharmaceutically acceptable carrier or diluent. In another embodiment, the invention features a pharmaceutical composition comprising siNA molecules of the invention, which can be chemically-modified, targeting one or more genes in a pharmaceutically acceptable carrier or diluent.

Exemplary active (with demonstrated *in vitro* activity according to **Example 5**) siRNA duplexes that meet the instant claim limitations are shown in **Figure 10**. See, for example, construct 30222/30224, corresponding to SEQ ID NOs: 373 and 374; construct 30222/30550, corresponding to SEQ ID NOs: 373 and 378; construct 30222/30555, corresponding to SEQ ID NOs: 373 and 379; and construct 30222/30556, corresponding to SEQ ID NOs: 373 and 380.

Additional exemplary active (with demonstrated *in vitro* activity according to **Example 5**) siRNA duplexes that meet the instant claim limitations are shown in **Figure 11**. See, for example, construct 30063/30430, corresponding to SEQ ID NOs: 372 and 375; construct 30431/30430, corresponding to SEQ ID NOs: 376 and 375; construct 30433/30430, corresponding to SEQ ID NOs: 377 and 375; and construct 30063/30224, corresponding to SEQ ID NOs: 372 and 374.

Exemplary active (with demonstrated *in vitro* activity according to **Example 5**) siRNA duplexes that meet the instant claim limitations are also shown in **Figure 12**. See, for example,

construct 30063/30224, corresponding to SEQ ID NOs: 372 and 374; and construct 30063/30430, corresponding to SEQ ID NOs: 372 and 375.

Exemplary active (with demonstrated *in vitro* activity according to **Example 5**) siRNA duplexes that meet the instant claim limitations are also shown in **Figure 13**. See, for example, construct 28251/30224, corresponding to SEQ ID NOs: 319 and 374; construct 30222/30224, corresponding to SEQ ID NOs: 373 and 374; construct 28251/30430, corresponding to SEQ ID NOs: 319 and 375; and construct 30222/30430, corresponding to SEQ ID NOs: 373 and 375.

Exemplary active (with demonstrated *in vitro* activity according to **Example 5**) siRNA duplexes that meet the instant claim limitations are further shown in **Figure 14**. See, for example, construct 30222/30546, corresponding to SEQ ID NOs: 373 and 386; construct 30222/30224, corresponding to SEQ ID NOs: 373 and 374; construct 30222/30551, corresponding to SEQ ID NOs: 373 and 387; construct 30222/30557, corresponding to SEQ ID NOs: 373 and 388; and construct 30222/30558, corresponding to SEQ ID NOs: 373 and 389.

Additional examples of active (with demonstrated *in vitro* activity according to **Example 5**) siRNA duplexes that meet the instant claim limitations are shown in **Figure 15**. See, for example, construct 30063/30430, corresponding to SEQ ID NOs: 372 and 375; construct 30434/30430, corresponding to SEQ ID NOs: 384 and 375; and construct 30435/30430, corresponding to SEQ ID NOs: 385 and 375.

Additional examples of active (with demonstrated *in vitro* dose response activity according to **Example 13**) siRNA duplexes that meet the instant claim limitations are shown in **Figure 26**. See, for example, construct 30612/30620, corresponding to SEQ ID NOs: 459 and 468; and construct 30612/31175, corresponding to SEQ ID NOs: 459 and 458.

Additional examples of active (with demonstrated *in vitro* duration activity out to 5 days according to **Example 13**) siRNA duplexes that meet the instant claim limitations are shown in **Figure 29**. See, for example, construct 30612/30620, corresponding to SEQ ID NOs: 459 and 468.

Additional examples of active (with demonstrated *in vitro* duration activity out to 5 days according to **Example 13**) siRNA duplexes that meet the instant claim limitations are shown in **Figure 30**. See, for example, construct 30612/31175, corresponding to SEQ ID NOs: 459 and 458.

Additional examples of active (with demonstrated *in vitro* dose response activity according to **Example 14**) siRNA duplexes that meet the instant claim limitations are shown in **Figure 39**. See, for example, construct 31456/31468, corresponding to SEQ ID NOs: 471 and 472; construct 31480/31492, corresponding to SEQ ID NOs: 473 and 474; and construct 31461/31473, corresponding to SEQ ID NOs: 475 and 476.

Additional examples of active (with demonstrated *in vitro* and *in vitro* dose response activity according to **Example 14**) siRNA duplexes that meet the instant claim limitations are shown in **Figures 40 and 41**. See, for example, construct 31344/30562, corresponding to SEQ ID NOs: 483 and 484; construct 31702/31706, corresponding to SEQ ID NOs: 487 and 488; construct 31703/31707, corresponding to SEQ ID NOs: 491 and 492; construct 31704/31708, corresponding to SEQ ID NOs: 495 and 496; and construct 31705/31709, corresponding to SEQ ID NOs: 499 and 500.

Additional examples of active (with demonstrated *in vitro* duration activity out to 21 days according to **Example 13**) siRNA duplexes that meet the instant claim limitations are shown in **Figures 77A-F**. See, for example, construct 30355/30366, corresponding to SEQ ID NOs: 441 and 442; construct 30612/31175, corresponding to SEQ ID NOs: 459 and 458; and construct 30612/30620, corresponding to SEQ ID NOs: 459 and 454.

Additional examples of active (with demonstrated *in vivo* activity in mice according to **Example 23**) siRNA duplexes that meet the instant claim limitations are shown in **Figures 80-83**. See, for example, construct 30612/30620, corresponding to SEQ ID NOs: 459 and 454.

Additional examples of active (with demonstrated *in vitro* dose response activity according to **Example 24**) siRNA duplexes that meet the instant claim limitations are shown in **Figure 84**. See, for example, construct 32636/32676, corresponding to SEQ ID NOs: 630 and 631; construct 32640/32680, corresponding to SEQ ID NOs: 632 and 633; and construct 32662/32702, corresponding to SEQ ID NOs: 634 and 635.

Additional examples of active (with demonstrated *in vitro* dose response activity according to **Example 24**) siRNA duplexes that meet the instant claim limitations are shown in **Figure 85**. See, for example, construct 32666/32706, corresponding to SEQ ID NOs: 636 and 637; and construct 32672/32712, corresponding to SEQ ID NOs: 638 and 639.

Additional examples of active (with demonstrated *in vitro* activity according to **Example 24**) siRNA duplexes that meet the instant claim limitations are shown in **Figure 86**. See, for

example, construct 31703/31707, corresponding to SEQ ID NOs: 491 and 492; construct 33193/33179, corresponding to SEQ ID NOs: 640 and 641; construct 33140/33180, corresponding to SEQ ID NOs: 642 and 643; construct 33145/33185, corresponding to SEQ ID NOs: 644 and 645; construct 33149/33183, corresponding to SEQ ID NOs: 646 and 647; construct 33150/33190, corresponding to SEQ ID NOs: 648 and 649; construct 33151/33191, corresponding to SEQ ID NOs: 650 and 651; and construct 33158/33187, corresponding to SEQ ID NOs: 652 and 653.

Additional examples of active (with demonstrated *in vitro* activity according to **Example 24**) siRNA duplexes that meet the instant claim limitations are shown in **Figure 87**. See, for example, construct 30612/30620, corresponding to SEQ ID NOs: 453 and 454; construct 33210/33250, corresponding to SEQ ID NOs: 654/655; construct 33212/33252, corresponding to SEQ ID NOs: 656 and 657; construct 33214/33254, corresponding to SEQ ID NOs: 658 and 659; construct 32429/32438, corresponding to SEQ ID NOs: 660 and 661; and construct 33226/33266, corresponding to SEQ ID NOs: 662 and 663.

In summary, detailed and comprehensive support for the presently claimed invention can be found in the paragraph on page 28, lines 12-29, the embodiments on page 56, the motifs of Table IV, ***over 150 exemplary sequences*** in Table I, and the Figures. Furthermore, experimental data obtained from ***over 50 siRNA molecules modified according to the instant claims indicated a clear capacity of these molecules to mediate RNA interference either in vitro or in vivo***. The proposed amendments therefore do not add new matter, and Applicants respectfully request their entry.

**Priority**

The Office declined to award the instant claims a priority that is earlier than the filing date of the instant application. *See,* Office Action, at pages 2-3. Applicants respectfully traverse.

At the outset, it is respectfully noted that the Examiner has misunderstood the claims as drawn to a duplex wherein "the sense strand is at least 10 nucleotides in length and the antisense strand is at least 20 nucleotides in length." Office action, at page 3. It is submitted that the use of the term "and" in amended part (c), previously part (b) of claim 52 is meant to indicate that the antisense strand can comprise 10 or more in total of modifications counting both 2'-O-methyl and 2'-fluoro modifications. In other words, the term "10 or more" modifies the term "2'-O-

methyl and 2'-deoxy-2'-fluoro," which is ***not*** meant to describe a construct having 10 or more 2'-O-methyl and 10 or more 2'-deoxy-2'-fluoro nucleotides.

To correct this misunderstanding, but without acquiescing to the Examiner's prior construction of the claims, Applicants have amended the instant claims to more clearly identify the modifications claimed therein. The amendments and instant claims are supported by all of the following priority applications: PCT/US03/05346, filed February 20, 2003, provisional application 60/408,378, filed September 5, 2002, and provisional application 60/358,580, filed February 20, 2002.

**PCT/US03/05346, filed on February 20, 2003, supports the instant claims as follows:**

The limitation of claim 52 part (a) *"each strand is between 18 and 27 nucleotides in length"* finds express support at page 22, lines 15-18:

> In another embodiment, a chemically-modified siNA molecule of the invention comprises a duplex having two strands, one or both of which can be chemically-modified, wherein each strand is about 18 to about 27 (*e.g.*, about 18, 19, 20, 21, 22, 23, 24, 25, 26, or 27) nucleotides in length…

The limitation of claim 52 part (b) *"the sense strand comprises 10 or more 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, or universal base modified nucleotides, and a terminal cap molecule at the 3'-end, the 5'-end, or both 3' and 5'-ends of the sense strand"* and part (c) *"the antisense strand comprises 10 or more 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, or universal base modified nucleotides"* and the limitations in dependant claims 53, 54, and 55 all find support in the paragraph bridging pages 19 and 20:

> In one embodiment, the invention features a siNA molecule, wherein the sense strand comprises one or more, for example, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more phosphorothioate internucleotide linkages, and/or one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or about one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the sense strand; and wherein the antisense strand comprises about 1 to about 10 or more, specifically about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more phosphorothioate internucleotide linkages, and/or one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the antisense strand. In another

embodiment, one or more, for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more, pyrimidine nucleotides of the sense and/or antisense siNA strand are chemically-modified with 2'-deoxy, 2'-O-methyl and/or 2'-deoxy-2'-fluoro nucleotides, with or without one or more, for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more, phosphorothioate internucleotide linkages and/or a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends, being present in the same or different strand.

Support for Claim 56 is found at page 42, line 28 to page 43, line 2:

In one embodiment, the invention features a composition comprising a siNA molecule of the invention, which can be chemically-modified, in a pharmaceutically acceptable carrier or diluent. In another embodiment, the invention features a pharmaceutical composition comprising siNA molecules of the invention, which can be chemically-modified, targeting one or more genes in a pharmaceutically acceptable carrier or diluent.

The present claims are also fully supported by the motifs of Table IV and in numerous exemplary sequences shown in Table I and the Figures of the PCT application, which discloses essentially the same sequences and experimental data as the instant application.

**Provisional application 60/408,378, filed September 5, 2002, supports the instant claims as follows:**

The limitation of claim 52 part (a) *"each strand is between 18 and 27 nucleotides in length"* finds support at page 15, lines 24-27:

In another embodiment, a chemically modified siRNA molecule of the invention comprises a duplex having two strands, one or both of which can be chemically modified, wherein each strand is between about 18 and about 27 (*e.g.*, about 18, 19, 20, 21, 22, 23, 24, 25, 26, or 27) nucleotides in length…

The limitation of claim 52 part (b) *"the sense strand comprises 10 or more 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, or universal base modified nucleotides, and a terminal cap molecule at the 3'-end, the 5'-end, or both 3' and 5'-ends of the sense strand"* and part (c) *"the antisense strand comprises 10 or more 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, or universal base modified nucleotides"* and the limitations in dependant claims 53, 54, and 55 all find support in the paragraph on page 13, lines 5-20:

In one embodiment, the invention features a siNA molecule, wherein the sense strand comprises one or more, for example, about 1, 2,

> 3, 4, 5, 6, 7, 8, 9, 10, or more phosphorothioate internucleotide linkages, and/or one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or about one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the sense strand; and wherein the antisense strand comprises about 1 to about 10 or more, specifically about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more phosphorothioate internucleotide linkages, and/or one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the antisense strand. In another embodiment, one or more, for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more, pyrimidine nucleotides of the sense and/or antisense siNA strand are chemically-modified with 2'-deoxy, 2'-O-methyl and/or 2'-deoxy-2'-fluoro nucleotides, with or without one or more, for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more, phosphorothioate internucleotide linkages and/or a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends, being present in the same or different strand.

Examples of sense strand sequences that meet the claim limitations can be found in Table I of the '378 provisional application. *See, e.g.,* SEQ ID NOs: 311, 312, 319, 329, 335, 339, 341, 343, 345, 372, 373, 376, 377, 382, 384, and 385. Examples of antisense strand sequences that meet the claim limitations can also be found in Table I. *See, e.g.,* SEQ ID NOs: 316, 317, 322, 332, 338, 340, 342, 344, 374, 375, 378, 379, 380, 381, 383, 386, 387, 388, and 389.

Support for claim 56 can be found at page 28, lines 11-16:

> In one embodiment, the invention features a pharmaceutical composition comprising a chemically modified siRNA molecule of the invention in a pharmaceutically acceptable carrier. In another embodiment, the invention features a pharmaceutical composition comprising chemically modified siRNA molecules of the invention targeting one or more genes in a pharmaceutically acceptable carrier.

Support for the instant claims is therefore found in numerous motifs and exemplary sequences shown in Table I and the Figures.

**Provisional application 60/358,580, filed February 20, 2002, supports the instant claims as follows:**

The limitation of claim 52 part (a) *"each strand is between 18 and 27 nucleotides in length"* finds support at page 11, lines 24-26:

> In another embodiment, a chemically modified siRNA molecule of the invention comprises a duplex having two strands, one or both of

which can be chemically modified, wherein each strand is between about 18 and about 27 nucleotides in length…

The limitation of claim 52 part (b) *"the sense strand comprises 10 or more 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, or universal base modified nucleotides, and a terminal cap molecule at the 3'-end, the 5'-end, or both 3' and 5'-ends of the sense strand"* and part (c) *"the antisense strand comprises 10 or more 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, or universal base modified nucleotides"* and the limitations in dependant claims 53, 54, and 55 all find support in the paragraph bridging pages 9 and 10:

> In one embodiment, the invention features a siRNA molecule, wherein the sense strand comprises one or more, for example about 1, 2, 3, 4, 5, 6, 7, 8 , 9 , or 10 phosphorothioate internucleotide linkages, and/or one or more 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or one or more universal base modified nucleotides, and optionally a terminal cap molecule at the 3', 5', or both 3' and 5'-ends of the sense strand; and wherein the antisense strand comprises any of between 1 and 10, specifically about 1, 2, 3, 4, 5, 6, 7, 8 , 9 , or 10 phosphorothioate internucleotide linkages, and/or one or more 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or one or more universal base modified nucleotides, and optionally a terminal cap molecule at the 3', 5', or both 3' and 5'-ends of the antisense strand. In another embodiment, one or more, for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 pyrimidine nucleotides of the sense and/or antisense siRNA stand are chemically modified with 2'-deoxy, 2'-O-methyl and/or 2'-deoxy-2'-fluoro nucleotides, with or without one or more, for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 phosphorothioate internucleotide linkages and/or a terminal cap molecule at the 3', 5', or both 3' and 5'-ends, being present in the same or different strand.

Examples of sense strand sequences that meet the claim limitations of claim 52 can be found in Table I of the '580 provisional application. *See, e.g.,* SEQ ID NOs: 315, 316, 323, 333, 339, 343, 345, and 347. Examples of antisense strand sequences that meet the claim limitations of claim 52 part (c) can also be found in Table I. *See, e.g.,* SEQ ID NOS: 320, 321, 326, 336, 342, 344, 346, and 348.

Support for claim 56 can be found at page 16, lines 26-30:

> In one embodiment, the invention features a pharmaceutical composition comprising a chemically modified siRNA molecule of the invention in a pharmaceutically acceptable carrier. In another embodiment, the invention features a pharmaceutical composition comprising chemically modified siRNA molecules of the invention targeting one or more genes in a pharmaceutically acceptable carrier.

Support for the instant claims is therefore found in numerous motifs and exemplary sequences shown in Table I and the Figures of the '580 application.

It should be noted that the term "siNA" is defined in the instant specification along with the term "siRNA," and these terms were fully intended to be interchangeably used with respect to the claimed double stranded molecules that mediate RNA interference. *See*, e.g., the instant specification, at page 67, line 24; PCT/US03/05346, at page 51, line 10; the '378 provisional application, at page 35, line 20; and the '580 provisional application, at page 20, line 26. Therefore, in view of the comprehensive disclosures of all claimed limitations in the instant application; the PCT application PCT/US03/05346, filed February 20, 2003; provisional application 60/408,378, filed September 5, 2002; and provisional application 60/358,580 filed February 20, 2002, the instant claims are entitled to a priority date of as early as February 20, 2002.

**Claim Rejections – 35 U.S.C.112, first paragraph, new matter**

The Office rejected claims 52-56 as allegedly containing new matter. *See,* Office Action, at pages 3-4. As explained in the above, the claims herein are fully supported by the instant specification and the priority applications. Applicants thus respectfully request that the new matter rejections be withdrawn.

**Claim Rejections – 35 U.S.C. 112, first paragraph, enablement**

The Office further rejected claims 52-56 as allegedly failing to provide enablement for "any nucleic acid molecule within the instant genus being active." Office Action, at page 5. Specifically, the Office stated that "one of skill would not be able to recognize that applicants was in possession of [] a huge genus of molecules that would act via RNAi with such variation in strand lengths and with no length limit and no specific stringency with a target sequence and such extensive modification." Office Action, at pages 6-7. The Office took issue with the number of species exemplified in the specification as "not demonstrative of any siRNA within the instant genus." Office Action, at page 7. Citing Elbashir, the Office particularly emphasized on the unpredictable compatibility of extensive modification with siRNA molecules. *Id.*

As discussed above, the instant claims have been amended herewith to include a strand length limitation as well as a set of more precisely defined combinations of modifications for each of the sense strand and the antisense strand, which together confer the capacity to mediate

RNA interference in extensively modified siRNA molecules. These limitations should obviate the Office's concern regarding the unpredictability of siRNA functions.

The unpredictability of activity in extensively modified siRNA molecules is correctly recognized by the Office. However, the Office's attention is respectfully directed to the fact that the instant specification and priority applications are replete with specific teachings and examples of ***extensively modified and active*** duplexes, which include combinations of 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and universal base modified nucleotides in the sense and antisense strands; phosphorothioate modified internucleotide linkages in the sense strand and/or antisense strand; and terminal cap modifications of the 3'-end, 5'-end, or both 3' and 5'-ends of the sense strand of the siRNA molecule. These combinations of different modifications have allowed for siRNA molecules to be extensively modified without abrogation of RNAi activity. ***There are over 150 sequences disclosed in the instant application encompassing the instantly claimed limitations.*** Furthermore, the instant application not only teaches one of skill in the art how to design, make, and use the instantly claimed modified siRNA, but also provides ***over 50 sets of experimental data indicating that extensively modified molecules according to the claimed structural features mediate RNA interference in vitro and/or in vivo***. See, for example, the numerous active siRNA constructs of **Figures 10, 11, 12, 13, 14, 15, 26, 29, 30, 39, 40, 41, 77, 80, 81, 82, 83, 84, 85, 86,** and **87,** as referred to above.

The Office indicates that "one skilled in the art could not predict a priori which species of molecules within the instant huge genus would in fact have RNAi activity." Office Action, at page 8. Applicants agree with the understanding that, before the time of the instant invention, one of skill in the art would not have had any reasonable expectation of success in practicing the instantly claimed invention. ***But following the extensive teaching in Applicants' applications, one of skill in the art would be able to make and use the entire genus of extensively and differentially modified siRNA molecules as claimed.*** This is because key structural features on which extensively modified siRNA with retained activity are premised have been clearly disclosed in the specification and figures, and have been included in the instant claims.

Therefore, any messenger RNA sequence, without *a priori* knowledge of the particular sequence, can be targeted for inhibition *via* RNAi using the enumerated constructs as presently claimed, although there may be circumstances under which non-optimal conditions may diminish efficacy or prevent cleavage of the target RNA. Under those circumstances, a skilled person in

the art can determine the more optimal conditions for RNAi activity by conducting the experiments taught in the instant specification. Thus, the instant claims are fully enabled and Applicants respectfully request withdrawal of the enablement rejections.

**Claim Rejections – 35 U.S.C. 103(a)**

The Office rejected claims 52-56 under 35 U.S.C. 103(a) as allegedly being obvious in view of Elbashir (EMBO J., 2001, 20(23):6877) in view of Nyce (WO 99/13886), Parrish (Molecular Cell, 6:1077-87, 2000), Matulic-Adamic (US 5,998,203), Bertrand (Biochemical & Biophysical Research Commun. 2002, 296:1000-1004); Braasch (Biochemistry, 2002, 41(14):4503-4510), and Olie (Biochimica et Biophysica Acta, 2002, 1576:101-109). Applicants respectfully traverse.

**RESPONSE TO THE EXAMINER'S ARGUMENTS**

In finding the claims obvious, the Examiner states that "one would have a reasonable expectation of success given that each of the modifications were known in the art at the time the invention was made to add benefits to antisense oligonucleotides, ribozymes or siRNA duplexes, as evidenced by Elbashir et al., Nyce, Matulic-Adamic et al., Parrish et al. and Olie et al., wherein each of the molecules face similar delivery challenges, and each of which can be improved with modifications, as evidenced by Braasch et al. Since Olie et al. teach effectively walking modifications across antisense oligonucleotides to optimize the combination of modifications as well as the location of the modifications and Elbashir et al. and Parrish et al. teach successfully synthesizing modified double stranded nucleic acid molecules, one would reasonably expect for modifications at various percentages to benefit the double stranded nucleoid acid molecules of Elbashir et al." Office action, at page 19.

Applicants respectfully traverse, and maintain that the presently claimed invention cannot be obvious for at least three reasons. First, Braasch, Bertrand, and Olie are not proper prior art references that could render the instant claims obvious because they were all published after the priority date to which the instant claims are entitled. Second, ***one of skill in the art would not have had any reasonable expectation of success in practicing the claimed invention at the time of the invention*** because the prior art either taught away from the claimed invention, or indicated a high level of unpredictability that would have precluded a reasonable expectation of success. Third, the Office is ***succumbing to impermissible hindsight*** in arguing that the present invention is obvious because it would be "obvious to try" the combinations of known modifications using

"routine optimization," even though the prior art gave "no direction as to which of many possible choices is likely to be successful" and offered "only general guidance as to the particular form of the claimed invention or how to achieve it." *See In re O'Farrell,* 853 F.2d 894, 903 (Fed. Cir. 1988)

***1. Priority***

As explained above, the instant claims are entitled to an early priority date of February 20, 2002, on which the U.S. Provisional Application 60/358,580 was filed. Therefore, at least Braasch *et al.* (published on April 9, 2002), Bertrand *et al.* (received on August 2, 2002) and Olie *et al.* (published July 19, 2002) are not proper prior references that should have been cited to render the instant claims obvious. As such, based on priority alone, the instant claims are not *prima facie* obvious.

***2. Unpredictability in extensively modified siRNA is recognized by the Office***

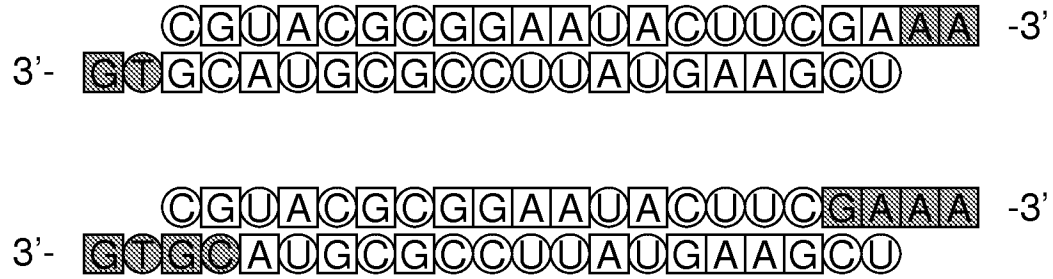
"As outlined above, it is well known that there is a high level of unpredictability in the RNAi art for extensively modifying siNA molecules that remain active" (Office action, page 8). It is respectfully submitted that the Office's recognition of unpredictability of RNAi activity in extensively modified siRNA molecules cannot be reconciled with the finding of obviousness in the instant claims. If it was unpredictable which of the extensively modified siRNA molecules might have activity, and if it would require undue experimentation to make each determination, then evidence of activity associated with a vast majority of short nucleotide duplexes modified according to the instantly claimed extensive modification patterns should be sufficient to demonstrate that the claims are not obvious over prior art. The instant Applicants provide such evidence, whereby the inclusion of specific combinations of different modifications in an siRNA molecule allows that molecule to be extensively modified and remain active. Simply stated, before Applicants invention, in view of the recognized unpredictability in extensive modification of siRNA, one of skill in the art would not have any reasonable expectation of success in practicing the instantly claimed invention. Therefore, the instant claims are not obvious.

***3. Key references taught away from the claimed invention and suggested a high level of unpredictability***

The instant claims recite short ***extensively modified*** nucleic acid duplexes with not only ***specific combinations of different modifications***, but also ***specific modification of certain well defined positions or nucleotide types***. For example, instant claim 52 recites terminal caps at

specific positions (3'-end, 5'-end, or both 3' and 5'-end positions of the sense strand), plus extensive modification (10 or more 2'-deoxy, 2'-O-methyl, 2'-fluoro or universal base modified nucleotides in both the sense strand and the antisense strand). Dependent claim 53 recites specific modifications of pyrimidine nucleotides. Claims 54 and 55 recite the further inclusion of up to 10 phosphorothioate modifications in the sense strand and antisense strand, respectively.

The closest prior art is the Elbashir reference cited herein. Elbashir taught that molecules that were "more extensively" modified than beyond up to four 3'-terminal nucleotides "reduce the ability of siRNAs to mediate RNAi, probably by interfering with protein association for siRNP assembly." *See* Elbashir, at page 6885, under "The siRNA user guide." Elbashir based this teaching or suggestion on experimental results obtained from the following constructs (wherein squares represent purine nucleotides (A or G) and circles represent pyrimidine nucleotides (U, C, or T); shaded regions represent 2'-deoxy nucleotides)):




Elbashir described the experimental results on pages 6881-6882, and in Figure 4, which are reproduced below:

> ***2'-deoxy- and 2'-O-methyl-modified siRNA duplexes***
> To assess the importance of the siRNA ribose residues for RNAi, duplexes with 21 nt siRNAs and 2 nt 3' overhangs with 2'-deoxy- or 2'-*O*-methyl-modified strands were examined (Figure 4). Substitution of the 2 nt 3' overhangs by 2'-deoxynucleotides had no effect and even the replacement of two additional ribonucleotides by 2'-deoxyribonucleotides adjacent to the overhangs in the paired region produced significantly active siRNAs. Thus, 8 out of 42 nt of a siRNA duplex were replaced by DNA residues without loss of activity. Complete substitution of one or both siRNA strands by 2'-deoxy residues, however, abolished RNAi, as did complete substitution by 2'-*O*-methyl residues.

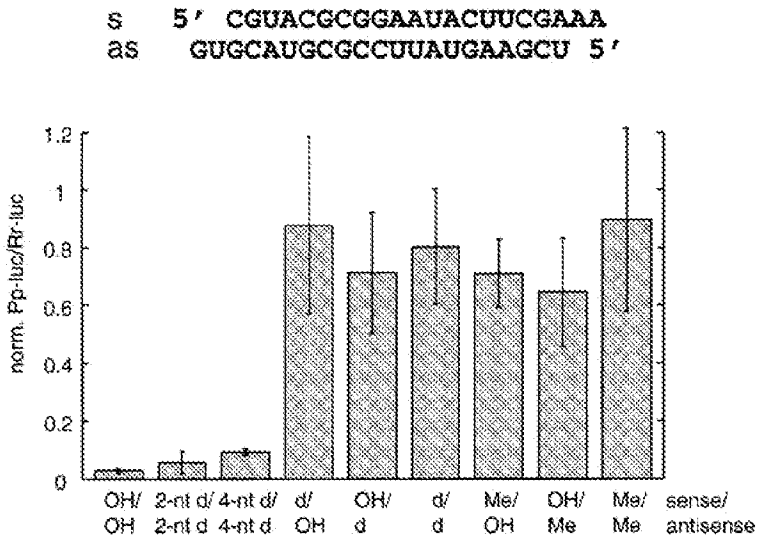



**Fig. 4.** Substitution of the 2′-hydroxyl groups of the siRNA ribose residues. The 2′-hydroxyl groups (OH) in the strands of siRNA duplexes were replaced by 2′-deoxy (d) or 2′-*O*-methyl (Me). 2 and 4 nt 2′-deoxy substitutions at the 3′ ends are indicated as 2- and 4-nt d, respectively. Uridine residues were replaced by 2′-deoxythymidine.

From these data, Elbashir expressly taught away from "more extensive modifications," as evidenced in the paragraph below reproduced from "The siRNA user guide:"

> ***The siRNA user guide***
>
> Efficiently silencing siRNA duplexes are composed of 21 nt sense and 21 nt antisense siRNAs and must be selected to form a 19 bp double helix with 2 nt 3'-overhanging ends. 2'-deoxy substitutions of the 2 nt 3'-overhanging ribonucleotides do not affect RNAi, but help to reduce the costs of RNA synthesis and may enhance RNase resistance of siRNA duplexes. ***More extensive 2'-deoxy or 2'-O-methyl modifications reduce the ability of siRNAs to mediate RNAi, probably by interfering with protein association for siRNP assembly.***

Therefore, the simple fact that the instant Applicants taught and claimed “more extensively” modified nucleic acid duplexes, i.e., molecules that are extensively modified beyond up to four 3’-terminal nucleotides and with more than a single type of modification (2'-deoxy), and which have demonstrated robust RNAi activity both *in vitro* and *in vivo* (*see* experimental results, such as those represented in Figures 10, 11, 12, 13, 14, 15, 26, 29, 30, 39, 40, 41, 77, 80, 81, 82, 83, 84, 85, 86, and 87 of the instant application), should indicate an unobvious invention achieved by following a path taught away by the prior art.

In this regard, the position taken by the Office that "Elbashir et al. are considered to offer motivation to incorporate chemical modifications at various percentages to optimize the activity of the duplex because not all modifications result in activity at every percentage" (Office Action, at page 20) cannot be reconciled with the clear warning against "more extensive modifications" in a "user guide" published by a leading group of researchers who pioneered early characterization of siRNAs. It is respectfully submitted that the Office appears to be picking and choosing portions while ignoring other parts of the references rather than looking at them as a whole. But this practice does not comport with a proper determination of obviousness, which requires that the prior art reference be considered in its entirety as a whole including portions that lead away from the claimed invention. MPEP § 2141.02, citing *W.L.Gore & Assoc. Inc. v. Garlock, Inc.*, 721 F.2d 1540 (Fed. Cir. 1983). Where an insight of an inventor is contrary to the understanding and expectations of the art, a structure effectuating it would not have been obvious. *Schenck v. Nortron Corp.*, 713 F.2d 283, 785 (Fed. Cir.1983). The Supreme Court in *KSR v. Teleflex,* 127 S. Ct. 1727 (2007) emphasized the key importance of a teaching away reference, stating that, "[w]hen the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious." *KSR,* at 1740 (citing *United States v. Adams*, 383 U.S. 39, 51-52 (1966)). Proceeding when there is a teaching away supports nonobviousness, not motivation. *See also*, MPEP §2145 ("proceeding contrary to accepted wisdom is evidence of nonobviousness").

Parrish, the only other RNAi-related references cited by the Office, disclosed certain chemical modifications, such as 2'-deoxy-2'-fluoro uridines, as compatible with RNAi activity in a long double stranded RNA (*unc-22,* which is 742 nt-long). There was no suggestion by Parrish that 2'-deoxy-2'-fluoro could be applied, with sustained RNAi activity, to other types of nucleotides (e.g., cytidines), or to short RNA duplexes. Importantly, Parrish taught away from incorporating 2'-deoxy modifications (as are presently claimed) because they were found to be detrimental to RNAi activity, a point that was entirely ignored by the Office. Specifically, Parrish described that modification of cytidine to deoxycytidine (or uracil to thymidine) on either the sense or the antisense strand produced substantial decrease in interference activity. *See* Parrish, at page 1081, right column. Parrish also taught away from applying more than one phosphorothioate modification to different nucleotide bases because more than one phosphorothioate base modification greatly reduced RNAi activity, and more than two

phosphorothioate base modifications abolished RNAi activity. *See* Parrish, at page 1084. Moreover, Parrish repeatedly stated that activity was more sensitive to modification of the antisense strand than modification of the sense strand. *See* Parrish, at page 1081, 1082 & 1084. Therefore, the fact that the instant Applicants taught and claimed extensively modified nucleic acid duplexes ***on both the sense and the antisense strands***, and which have demonstrated robust RNAi activity (see experimental results such as those represented in Figures 10, 11, 12, 13, 14, 15, 26, 29, 30, 39, 40, 41, 77, 80, 81, 82, 83, 84, 85, 86, and 87 of the instant application), should be yet another indication that an unobvious invention was achieved by following a path taught away by Parrish.

In fact, the cited references provided clear evidence that it ***was highly unpredictable*** at the time of the present invention as to whether and how the chemical modifications that had been developed for antisense and ribozyme fields might be applicable to siRNA molecules without abrogating RNAi activity. Specifically, it must first be noted that the Office misread Matulic-Adamic as teaching or directing those skilled in the art to modify, with the terminal cap moieties, a ***double-stranded*** nucleic acid structure as claimed herein. *See* Office Action, at page 12 ("Matulic-Adamic et al. teach chemical modifications of double stranded nucleic acid structures."). On the contrary, the nucleic acid molecules of Matulic-Adamic are all ***single-stranded*** ribozyme oligonucleotides that have secondary structures, such as stem loop regions. These stem loop regions are the only possible basis for double-stranded structures being disclosed in Matulic-Adamic. However, none of these secondary structures have more than 5-base pairs; none have complementarity to a target RNA; and none have terminal cap modifications at the 3' and 5'-ends. In fact, inclusion of the instantly claimed features in the stem loop regions of the Matulic-Adamic ribozymes would be physically impossible, as these stem loop regions are secondary structures that arose from folding a ***single strand***. Therefore, any guidance as to predictability with respect to the terminal caps and other chemical modification strategies taught by Matulic-Adamic is limited to use in single-stranded ribozymes to support ribozyme catalysis. Likewise, it should be noted that Olie's and/or Nyce's teaching of chemical modifications were limited to antisense gapmers, which are also clearly single-stranded constructs. Nowhere in Olie or Nyce[1] was any mention that the chemical modifications

[1] It appears that the Office read the antisense gapmer of Nyce as including a combination of 2'-deoxy and 2'-O-methyl modifications. *See* Office Action, at page 11. This reading is incorrect, however, because antisense

described therein can be suitable or beneficial for molecules other than single-stranded gapmers that have, when base-paired to a target mRNA, become RNAse H substrates. Therefore, unless there was teaching in the art to indicate that modifications previously known to be applicable to a single-stranded ribozyme (such as those in Matulic-Adamic), or a single-stranded antisense nucleotide (such as those in Olie or Nyce) can be ***predictably*** applied to a double-stranded siRNA molecule without abrogating RNAi activity, the skilled person in the art was faced with no reasonable expectation of success in applying any of the stabilizing modifications disclosed in Matulic-Adamic or Olie/Nyce to an siRNA molecule, let alone in using of such modifications both extensively and in certain specific combinations.

The closest prior art, Elbashir, taught only limited modification of the 3'-terminal overhangs with a single type of modification, and warned against "more extensive modifications." While generically suggesting the use of 2'-deoxy modification (to stabilize the 3'-overhangs of an siRNA molecule), Elbashir was unequivocal in stating that "[c]omplete substitution of one or both siRNA strands by 2'-deoxy residues, however ***abolished*** RNAi, as did substitution by 2'-O-methyl residues." *See* Elbashir, at page 6882. Elbashir also expressly stated that, while 2'-deoxy substitution of the 3'-overhang ribonucleotides does not affect RNAi, "[m]ore extensive 2'-deoxy or 2'-O-methyl modifications, however, reduce the ability of siRNAs to mediate RNAi." *See* Elbashir, at page 6885. It would not have escaped the notice of a skilled person in the art that ***all*** of the Elbashir modifications that could lead to abolished RNAi activity if applied too much or at the wrong positions, i.e., 2'-deoxy and 2'-O-methyl used either in internal positions or 5'-terminal positions, were those found to be generically "beneficial" to the other single-stranded molecules. For example, 2'-O-methyl modifications were found to benefit

---

molecules of Olie or Nyce inhibit gene expression by an RNase H mechanism, wherein the enzyme RNase H recognizes and cleaves the mRNA target in an RNA:DNA duplex. *See, generally, chapter 6.4 Optimizing Oligonucleotide Drugs, 6.4.2.1., Gapmer Designs,* pages 169-170, Antisense Drug Technology, Principles, Strategies, and Applications, Crooke ed., 2nd ed. CRC Press (2006) (copy attached). Thus, an antisense gapmer molecule in its native and unmodified form has at least a DNA region that would form a duplex with the mRNA target, which allows for the recruitment of RNase H and knockdown of gene expression. In a chimeric or "gapmer" construct, such as the ones described in Olie or Nyce, the ends of the antisense strand, or the "wings" can be modified to enhance stability, but even in Olie and Nyce, the wings of each molecule are modified with a single type of 2'-sugar modification. Here, because those skilled in the siRNA art were seeking to modify an interfering duplex that clearly did not function *via* an RNase H mechanism, there would be no reason to include an internal stretch of DNA in an siRNA molecule stabilized on the ends.

the Olie/Nyce gapmers; and 2'-deoxy, 2'-fluoro, and 2'-O-methyl modifications were found to benefit the Matulic-Adamic ribozymes.

Parrish suggested the same lack of predictability. Indeed, it repeatedly taught that RNAi activity was more sensitive to modification of the antisense strand than modification of the sense strand, and that depending on the type and location of the modification, inactivity would result. *See* Parrish, at pages 1081, 1082 & 1084. Therefore Parrish confirmed that the use of known modifications from other nucleotide arts, such as antisense and ribozyme applications, led to unpredictable results in RNAi applications at the time of its publication. Moreover, as discussed at length above, Parrish effectively taught away from using 2'-deoxy modification and phosphorothioate modifications, even though these modifications were found to be generically beneficial to the gapmers of Olie/Nyce and to the ribozymes of Matulic-Adamic. Thus, known modifications that were applicable and/or beneficial to single-stranded antisense molecules (such as 2'-O-methyl modifications, according to Olie and/or Nyce), and to single-stranded ribozymes (such as 2'-deoxy, 2'-fluoro, and 2'-O-methyl modifications, according to Matulic-Adamic) were ***often*** found to be detrimental to double-stranded RNA molecules. In fact, in all instances but one (i.e., 2'-deoxy modifications on 3'-overhang plus two immediately adjacent nucleotides), the beneficial effect of improved stability was severely tempered by the loss of RNAi activity. In this regard, the present invention drawn to extensively and differentially modified short double-stranded nucleic acid molecules having robust RNAi activity does indeed provide surprising and an unexpected result in view of the state of the art at the time. Therefore, a person skilled in the art at the time of the present invention was faced with a complete lack of predictability and no reasonable expectation of success to apply modifications developed for the antisense and ribozyme applications to an siRNA as presently claimed.

***4. "Obvious to try" analysis under In re Kubin in view of In re O'Farrell also precludes a finding of obviousness***

In supporting a finding of obviousness, the Office argued for a reasonable expectation of success "[g]iven that each of the modifications were known in the art at the time the invention was made to benefit nucleic acid stability, and it was known to incorporate the same modifications from antisense/ribozyme technology into siRNAs" and that "it would have been obvious to incorporate the instant modifications into at least 10 nucleotides of the sense strand or twenty nucleotides of the antisense strand in combination with the specification modification of

10 or more pyrimidines and this is considered within the realm of routine optimization." Office Action, at page15. At the outset, it should be noted that Applicants are not claiming the method of applying modifications to siRNA using "routine optimization." The Office is essentially arguing that the present invention would be "obvious to try" using known modifications and routine experimentation. Applicants respectfully disagree.

The Federal Circuit recently clarified the standard for finding obviousness based on "obvious to try" in *In re Kubin*, 561 F.3d 1351, 1359 (Fed. Cir. 2009). While acknowledging that, as stated by the U.S. Supreme Court in *KSR,* a skilled artisan, when motivated by an unmet need, can look to combine elements within the scope of the prior art, it would be improper to hold a claim obvious when:

> what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result; where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful

or

> what was "obvious to try" was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.

To hold a claim obvious under these situations would be, according to the Federal Circuit, "succumb[ing] to hindsight claims of obviousness" and erroneous. *Id.* Reaffirming its prior holdings in *O'Farrell*, the Federal Circuit explained that in order for an "obvious to try" situation to serve as the basis for obviousness, some direction in the prior art that would provide a reasonable expectation of success is still required. *See O'Farrell,* at 903-04.

It should first be noted that the instant claims are drawn to molecules that combine different types of modifications at different positions of the siRNA. For example, claim 52 recites not only modifications at particular positions, *i.e.,* terminal cap modifications at the 3'-end, 5'-end, or both the 3' and 5' ends of the sense strand, but also extensive modification with specific types: 10 or more 2'-deoxy, 2'-fluoro, 2'-O-methyl, or universal base modified nucleotides in the sense and antisense strands. There is nothing in the cited references that could have been taken to suggest a combined application of 5'- and 3-terminal cap modifications of the sense strand with 10 or more modified (with 2'-deoxy, 2'-fluoro, 2'-O-methyl or universal base) nucleotides in the sense and antisense strands in an siRNA context. As explained above, the Olie

and Nyce references are drawn to antisense gapmers, and all of the modifications disclosed therein, ***which do not include terminal cap modifications,*** were specifically developed for antisense molecules to recruit RNAase H when base paired to an RNA. Matulic-Adamic is drawn to a hammerhead ribozyme, and all of the modifications disclosed therein were specifically developed to improve stability of the largely single-stranded construct while supporting the catalytic activity of the ribozyme. There was no indication whatsoever from either Olie/Nyce or Matulic-Adamic that these modifications could be applied to a short nucleic acid duplex without abrogating RNAi activity.

Elbashir does not teach or suggest the combination of modifications from ribozyme and antisense art. In fact, each of the chemically modified Elbashir siRNA molecules, ***active or not,*** contained a single type of modification. It was either a 2'-deoxy, or a 2'-O-methyl. None of the molecules in that reference contained or even contemplated a terminal cap moiety, let alone putting a terminal cap moiety on both ends of the sense strand, in addition to 10 or more 2'-deoxy, 2'-fluoro, or 2'-O-methyl modified pyrimidine nucleotides in the sense and antisense strands. Likewise, Parrish did not teach molecules that were modified with more than a single type of modification. All of the modified molecules therein, ***active or not,*** contained a single type of modification. Again, a terminal cap moiety was not even contemplated. Therefore, the prior art did not provide or indicate any direction as to which of the many possible choices would likely lead to success.

On the other hand, it should be noted that those skilled in the art of siRNA and RNA interference had plenty of stabilizing modifications to choose from, even if they ignore the huge body of research literature on nucleotide-based gene inhibitors and focus on only the references cited by the Office. However, none of the cited references provided any guidance on how to apply modifications to siRNA and retain RNAi activity with any level of predictability to support a reasonable expectation of success. For example, while the Office selectively cited to its teaching of modifying antisense molecules with phosphorothioate, 2'-deoxy and 2'-O-methyl, Nyce's disclosure is much more:

> The analogue heteroaromatic bases may be selected from all pyrimidines and purines, which may be substituted by O, halo, $NH_2$, SH, SO, $SO_2$, $SO_3$, COOH and branched and fused primary and secondary amino, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkoxy, alkenoxy, acyl, cycloacyl, arylacyl, alkynoxy, cycloalkoxy, aroyl, arylthio, arylsulfoxyl, halocycloalkyl, alkylcycloalkyl, alkenylcycloalkyl, alkynylcycloalkyl, haloaryl, alkylaryl, alkenylaryl, alkynylaryl,

arylalkyl, arylalkenyl, arylalkynyl, arylcycloalkyl, which may be further substituted by O, halo, $NH_2$, primary, secondary and tertiary amine, SH, SO, $SO_2$, $SO_3$, cycloalkyl, heterocycloalkyl and heteroaryl. The pyrimidines and purines may be substituted at all positions as is known in the art, but preferred are those which are substituted at positions 1, 2, 3, 4, 7 and/or 8. More preferred are pyrimidines and purines such as theophylline, caffeine, dyphylline, etophylline, acephylline piperazine, bamifylline, enprofylline and xantine having the chemical formula [formula omitted], wherein $R^1$ and $R^2$ are independently H, alkyl, alkenyl or alkynyl and $R^3$ is H, aryl, dicycloalkyl, dicycloalkenyl, dicycloalkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, O- cycloalkyl, O-cycloalkenyl, O-cycloalkynyl, $NH_2$-alkylamino-ketoxyalkyloxy-aryl, mono and dialkylaminoalkyl-N-alkylamino-$SO_2$ aryl, among others.

Nyce, at page 10, lines 5-21.

Preferred backbone analogue residues include phosphorothioate, methylphosphonate, phosphotriester, thioformacetal, phosphorodithioate, phosphoramidate, formacetal boranophosphate, 3'-thioformacetal, 5'-thioether, carbonate, 5'- N-carbamate, sulfate, sulfonate, sulfamate, sulfonamide, sulfone, sulfite., 2'-O methyl, sulfoxide, sulfide, hydroxylamine, methylene(methylimino) (MMI), and methyleneoxy(methylimino) (MOMI) residues. Phosphorothioate and methylphosphonate- modified oligonucleotides are particularly preferred due to their availability through automated oligonucleotide synthesis.

Nyce, at page 15, lines 29-36. It is particularly noted that all of the above-listed modifications were said to confer stability, RNA affinity, and in the case of backbone modifications, also cellular permeation.

Adding to this already large list of modifications, Matulic-Adamic, an application drawn to ribozyme-based gene inhibitors, discloses others:

In a second aspect, the invention features enzymatic nucleic acids with 5'-end modifications (5'-cap) having the formula: [Formula omitted] wherein, X represents H, alkyl, amino alkyl, hydroxy alkyl, halo, trihalomethyl [$CX_3$ (X=Br, Cl, F)], $N_3$, $NH_2$, NHR, $NR_2$ [each R is independently alkyl (C1-22), acyl (C1-22), or substituted (with alkyl, amino, alkoxy, halogen, or the like) or unsubstituted aryl], $NO_2$, $CONH_2$, COOR, SH, OR, ONHR, $PO_4^{2-}$, $PO_3S^{2-}$, $PO_2S_2^{2-}$, $POS_3^{2-}$, $PO_3NH_2^-$, $PO_3NHR^-$, $NO_2$, $CONH_2$, COOR, B represents a natural base or a modified base or H; Y represents rest of the enzymatic nucleic acid; and $R^1$ represents H, O-alkyl, C-alkyl, halo, NHR, or $OCH_2SCH_3$ (methylthiomethyl). The 5'-modified sugar synthesis is as described by Moffatt, in Nucleoside Analogues:Chemistry, Biology and Medical Applications, Walker, DeClercq, and Eckstein, Eds,; Plenum Press:New York, 1979, pp 71 (incorporated by reference herein).

Another preferred embodiment of the invention features enzymatic nucleic acid molecules having a 5'-cap, wherein said cap is selected from but not limited to, a group comprising, 4',5'-methylene nucleotide; 1-(β-D-erythrofuranosyl)nucleotide; 4'-thio nucleotide, carbocyclic nucleotide; 5'-amino-alkyl phosphate; 1,3-diamino-2-propyl phosphate, 3-aminopropyl phosphate; 6-aminohexyl phosphate; 12-aminododecyl

phosphate; hydroxypropyl phosphate; 1,5-anhydrohexitol nucleotide; L-nucleotide; α-nucleotide; modified base nucleotide; phosphorodithioate; threo-pentofuranosyl nucleotide; acyclic 3',4'-seco nucleotide; 3,4-dihydroxybutyl nucleotide; 3,5-dihydroxypentyl nucleotide, 5'-5'-inverted nucleotide moeity; 5'-5'-inverted abasic moeity; 5'-phosphoramidate; 5'-phosphorothioate; 1,4-butanediol phosphate; 5'-amino; bridging and/or non-bridging 5'-phosphoramidate, phosphorothioate and/or phosphorodithioate, bridging or non bridging methylphosphonate and 5'-mercapto moeities (for more details see Beaucage and Lyer, 1993, Tetrahedron 49, 1925; incorporated by reference herein).

In a third aspect, the invention features enzymatic nucleic acids with 3'-end modifications (3'-cap) having the formula: [Formula omitted] wherein, X represents 4'-thio nucleotide, carbocyclic nucleotide; 1,5-anhydrohexitol nucleotide; L-nucleotides; α-nucleotides; modified base nucleotide; phosphorodithioate linkage; threo-pentofuranosyl nucleotide; acyclic 3',4'-seco nucleotide; acyclic 3,4-dihydroxybutyl nucleotide; acyclic 3,5-dihydroxypentyl nucleotide, 3'-3'-inverted nucleotide moeity; 3'-3'-inverted abasic moeity; 3'-2'-inverted nucleotide moeity; 3'-2'-inverted abasic moeity; 1,4-butanediol; 3'-phosphoramidate; hexylphosphate; aminohexyl phosphate; 3'-phosphate; 3'-phosphorothioate; or bridging or nonbridging methylphosphonate moeity; B represents a natural base or a modified base or H; Y represents rest of the enzymatic nucleic acid; and R1 represents H, O-alkyl, C-alkyl, halo, NHR [R=alkyl (C1-22), acyl (C1-22), substituted or unsubstituted aryl], or $OCH_2SCH_3$ (methylthiomethyl).

In yet another preferred embodiment the invention features enzymatic nucleic acid molecules having a 3'-cap, wherein said cap is selected from but not limited to, a group comprising, 4'-thio nucleotide, carbocyclic nucleotide; 1,5-anhydrohexitol nucleotide; L-nucleotides; α-nucleotides; modified base nucleotide; phosphorodithioate linkage; threo-pentofuranosyl nucleotide; acyclic 3',4'-seco nucleotide; acyclic 3,4-dihydroxybutyl nucleotide; acyclic 3,5-dihydroxypentyl nucleotide, 3'-3'-inverted nucleotide moeity; 3'-3'-inverted abasic moeity; 3'-2'-inverted nucleotide moeity; 3'-2'-inverted abasic moeity; 1,4-butanediol phosphate; 3'-phosphoramidate; hexylphosphate; aminohexyl phosphate; 3'-phosphate; 3'-phosphorothioate; phosphorodithioate; or bridging or nonbridging methylphosphonate moeity (for more details see Beaucage and lyer, 1993, Tetrahedron 49, 1925; incorporated by reference herein).

Matulic-Adamic, column 2, lines 47-49; column 4, line 62, to column 5, line 22. Indeed, the terminal modifications alone include a dense list spanning at least an entire column in the printed patent. As such, it can be safely concluded that the skilled person in the art at the time of the present invention was faced with an enormous list of stabilizing chemical modifications but no direction as to which among these could be applied to an siRNA molecule without abrogating activity.

Faced with the large number of known chemical modifications, which were taught by the references to be "beneficial" to gapmers and ribozymes, the skilled person in the art is provided no guidance as to what specific combinations of modifications to use extensively with an siRNA

molecule to produce one that is both active and stable. As explained above, the key references (Elbashir and Parrish) all indicated that extensive incorporation of modifications into an siRNA was detrimental, or at least highly unpredictable. Bertrand does not even disclose an siRNA molecule that is chemically modified, and nor does Braasch. The mention in those articles that "good uptake" is key to the success of siRNA technology does nothing to point the way for those skilled in the art to a few specific modifications, among the vast list of potentially uptake-enhancing or otherwise beneficial modifications above. Indeed, neither article provides any teaching that the instantly claimed combinations of modifications are the ones that will lead to good uptake or even the ones to try. Thus, to arrive at the presently claimed invention would clearly require extensive combination and testing of all known modifications, even though the particular ones that were selected by the instant Applicants were actually those that were taught by the cited references to be often detrimental when applied "more extensively." As such, one of skill in the art would simply have ***no reasonable expectation of success*** in practicing the claimed invention.

Finally, even if one takes the position that routine testing with known modifications and known assays would ***eventually*** lead one of skill in the art to the presently claimed invention, this would be insufficient to establish a *prima facie* case of obviousness for at least two reasons. First, the references cited by the Office fails to give any indication of which parameters were critical to success, and in many instances taught away from the claimed modifications. Second, at the time of the present invention, RNAi was a new technology and the experiences of the antisense/ribozyme arts at most gave general guidance as to types of modifications one could apply to an siRNA molecule, providing merely a large toolbox of possibilities. But these known modifications were individually demonstrated by those who first studied siRNAs in the field to be sometimes feasible, but ***more often than not incompatible*** with RNAi activity. That unpredictability grows only larger if the known modifications were applied extensively, and in combination. Thus, numerous types of modifications were known in the art such that this was not a case of testing a finite number of identified, predictable solutions. "In such circumstances, where a defendant merely throws metaphorical darts at a board filled with combinatorial prior art possibilities, courts should not succumb to hindsight claims of obviousness." *Kubin,* at 1359.

Therefore, this is not an instance where the prior art "contained detailed enabling methodology for practicing the claimed invention, a suggestion to modify the prior art to practice

the claimed invention, ***and evidence suggesting that it would be successful.***" Rather, it is an instance where the prior art provides "no direction as to which of many possible choices is likely to be successful" and "only general guidance as to the particular form of the claimed invention or how to achieve it." Most importantly, the prior art, by teaching that either (1) more extensive modification, or (2) differential modification is detrimental (in all instances examined), precludes any reasonable expectation of success in practicing the claimed invention, which calls for both (1) more extensive modification and (2) differential modification. Applicants' arguments do not rest on an absolute predictability of success, but rather point to a fundamental lacking of even a reasonable expectation of success. Any finding of obviousness under the "obvious to try" standard is therefore improper under the jurisprudence of *Kubin* and *O'Farrell*.

Thus, the pending claims are not *prima facie* obvious over the cited references and Applicants respectfully request withdrawal of the obviousness rejections.

**Claim rejections – Double Patenting**

The Office provisionally rejected claims 52-56 as allegedly being unpatentable on the ground of non-statutory obviousness-type double patenting over claims 1-5 and 8-21 of copending Application No. 11/502,876, and claims 1, 2, 5-9, 11, 13, 14 and 17-31 of copending application 11/502,893. *See* Office Action, at page 21. The Office also provisionally rejected claims 52-56 as allegedly being unpatentable on the same ground over claims 1-20 of copending Application No. 12/170,290; claims 1-20 of copending Application No. 12/185,652; claims 1-20 of copending Application No. 12/204,572; claims 1-20 of copending Application No. 12/203,055; claims 1-20 of copending Application No. 12/200,736; claims 1-20 of copending Application No. 12/203,731; claims 1-20 of copending Application No. 12/204,612; claims 1-20 of copending Application No. 12/175,367; and claims 129-138 of copending Application No. 10/444,853.

It is respectfully noted that as of April 28, 2009, Application No. 11/502,893 has been abandoned. As such, the '893 application is no longer a co-pending application, and the ODP rejections on its basis should be withdrawn.

Applicants respectfully request that the Examiner hold the other provisional double-patenting rejections in abeyance until such time when they become the sole remaining rejections in the instant application. Applicants then request that these rejections be withdrawn in accordance with MPEP § 804 I.B., which states:

*If the "provisional" ODP rejections in two applications are the only rejections remaining in those applications, the examiner should then withdraw the ODP rejection in the earlier filed application thereby permitting that application to issue without need of a terminal disclaimer.*

As explained above, the instant application has the same effective priority date as its parent application, USSN 10/444,853, on which one of the provisional ODP rejections has been based.

Applicants will consider filing one or more terminal disclaimer, if appropriate, when the instant claims are held otherwise allowable.

**Conclusion**

In view of the foregoing, Applicants respectfully submit the pending claims are in condition for allowance but for the residual provisional double-patenting issues. If the Examiner believes a telephone conference would expedite prosecution of this application, she is urged to telephone the undersigned at the telephone number below.

Respectfully submitted,
Merck & Co., Inc.

Date: September 18, 2009

/Wenfang Chen/
Wenfang Chen
Registration No. 52,729

1700 Owens Street, 4th Floor
San Francisco, CA 94158
Phone: 415-814-8422
Email: wenfang_chen@merck.com